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| FORM PTO-1390 U.S. Department of Commerce Patent and Trademark Office | | Attorney's Docket No. 3240-109 |
| TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371 | | U.S. Application No. (if known) <div style="font-size: 1.5em; font-weight: bold;">10/559649</div> |
| INTERNATIONAL APPLICATION NO. PCT/SG2004/000168 | INTERNATIONAL FILING DATE June 4, 2004 | PRIORITY DATE CLAIMED June 5, 2003 |
| TITLE OF INVENTION Cholesterol Biosynthesis Pathway Modulators and Uses Thereof | | |
| APPLICANT(S) FOR DO/EO/US Kandiah JEYASEELAN, Arunmozhiarasi ARMUGAM, Siaw Ching CHAI, Prabhakaran Nair RAMKISHEN, Ponnampalam GOPALAKRISHNAKONE, Kwong Huat, Benny TAN | | |
| Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information: | | |
| <ol style="list-style-type: none"> 1. <input checked="" type="checkbox"/> This is a FIRST submission of items concerning a filing under 35 U.S.C. 371 2. <input type="checkbox"/> This is a SECOND or SUBSEQUENT submission of items concerning a filing under 35 U.S.C. 371. 3. <input type="checkbox"/> This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include items (5), (6), (9) and (21) indicated below. 4. <input checked="" type="checkbox"/> The US has been elected (Article 31). 5. <input checked="" type="checkbox"/> A copy of the International Application as filed (35 U.S.C. 371(c)(2)) <ol style="list-style-type: none"> a. <input type="checkbox"/> is attached hereto (required only if not communicated by the International Bureau). b. <input checked="" type="checkbox"/> has been communicated by the International Bureau. c. <input type="checkbox"/> is not required, as the application was filed in the United States Receiving Office (RO/US) 6. <input type="checkbox"/> An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)). <ol style="list-style-type: none"> a. <input type="checkbox"/> is attached hereto. b. <input type="checkbox"/> has been previously submitted under 35 U.S.C. 154(d)(4). 7. <input checked="" type="checkbox"/> Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3)) <ol style="list-style-type: none"> a. <input type="checkbox"/> are attached hereto (required only if not communicated by the International Bureau). b. <input type="checkbox"/> have been communicated by the International Bureau. c. <input type="checkbox"/> have not been made; however, the time limit for making such amendments has NOT expired. d. <input checked="" type="checkbox"/> have not been made and will not be made. 8. <input type="checkbox"/> An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)). 9. <input checked="" type="checkbox"/> An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)). 10. <input type="checkbox"/> An English language translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)). | | |
| ITEMS 11. TO 20. below concern other document(s) or information included: | | |
| <ol style="list-style-type: none"> 11. <input checked="" type="checkbox"/> An Information Disclosure Statement under 37 CFR 1.97 and 1.98. 12. <input type="checkbox"/> An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included. 13. <input checked="" type="checkbox"/> A preliminary amendment. 14. <input checked="" type="checkbox"/> An Application Data Sheet under 37 CFR 1.76. 15. <input type="checkbox"/> A substitute specification. 16. <input type="checkbox"/> A power of attorney and/or change of address letter. 17. <input type="checkbox"/> A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821-1.825 18. <input type="checkbox"/> A second copy of the published international application under 35 U.S.C. 154(d)(4). 19. <input type="checkbox"/> A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4). | | |

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| U.S. APPLICATION NO. (if known) | INTERNATIONAL APPLICATION NO. PCT/SG2004/000168 | ATTORNEY DOCKET NO. 3240-109 |
| 20. <input checked="" type="checkbox"/> Other items or information: Written Opinion of the International Preliminary Examining Authority, Written Opinion of the International Searching Authority Response to the Written Opinion International Preliminary Report on Patentability Published Application WO/ 2004/10928 A1 with International Search Report | | |
| 21. The following fees are submitted: | | CALCULATIONS |
| <input checked="" type="checkbox"/> Basic National Fee \$300.00 | | PTO USE ONLY |
| 22. <input checked="" type="checkbox"/> Examination Fee If the written opinion prepared by ISA/US or the IPER prepared by IPEA/US indicates all claims satisfy provisions of PCT Article 33(1)-(4) \$0 All other situations \$200.00 | | \$ 200.00 |
| 23. <input checked="" type="checkbox"/> Search Fee If the written opinion of the ISA/US or the IPER prepared by IPEA/US indicates all claims satisfy provisions of PCT Article 33(1)-(4) \$0 Search fee (37 CFR 1.445(a)(2)) has been paid on the international application to the USPTO as an International Search Authority \$100.00 International Search Report prepared by an ISA other than the US and provided to the Office or previously communicated to the US by the IB \$400.00 All other situations \$500.00 | | \$ 400.00 |
| TOTAL OF 21, 22 AND 23 = | | \$ 900.00 |
| <input type="checkbox"/> Additional fee for specification and drawings filed in paper over 100 (excluding sequence listing or computer program listing filed in an electronic medium). The fee is \$250.00 for each additional 50 sheets of paper or fraction thereof. | | \$ |
| Total Sheets | Extra Sheets | Number of each additional 50 or fraction thereof |
| - 100 = | / 50 = | x 250 |
| Surcharge of \$130.00 for furnishing any of the search fee, examination fee, or the oath or declaration later than 30 months from the earliest claimed priority date (37 CFR 1.492(h)). | | \$ |
| Claims | Number Filed | Number Extra |
| Total Claims | 38 - 20 = | 8 |
| Independent Claims | 6 - 3 = | 3 |
| Multiple dependent claim(s) (if applicable) | | + \$360.00 |
| TOTAL OF ABOVE CALCULATIONS = | | \$ 1,900.00 |
| <input checked="" type="checkbox"/> Applicant claims small entity status. The fees indicated above are reduced by 1/2. | | \$ 950.00 |
| SUBTOTAL = | | \$ 950.00 |
| Processing fee of \$130.00 for furnishing the English translation later than 30 months from the earliest claimed priority date (37 CFR 1.492(f)). | | + |
| TOTAL NATIONAL FEE = | | \$ 950.00 |
| Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). \$40.00 per property | | + |
| TOTAL FEES ENCLOSED = | | \$ 950.00 |
| | | Amount to be refunded |
| | | \$ |
| | | Amount to be charged |
| | | \$ |

10/559649

IAP9 Rec'd PCT/PTO 05 DEC 2003

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| U.S. APPLICATION NO. (if known) | INTERNATIONAL APPLICATION NO. PCT/SG2004/000168 | ATTORNEY DOCKET NO. 3240-109 |
| <p>a. <input type="checkbox"/> A check in the amount of \$_____ to cover the above fees is enclosed.</p> <p>b. <input checked="" type="checkbox"/> Please charge my Deposit Account No. 02-2135 in the amount of \$ <u>950.00</u> to cover the above fees. A duplicate copy of this sheet is enclosed.</p> <p>c. <input checked="" type="checkbox"/> The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 02-2135. A duplicate copy of this sheet is enclosed.</p> <p>NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.</p> <p>SEND ALL CORRESPONDENCE TO:</p> <p>Customer No. 06449</p> <p>Barbara G. Ernst Rothwell, Figg, Ernst & Manbeck 1425 K St., N.W. Washington, D.C. 20005 Phone: 202/783-6040</p> <p><u>Barbara G Ernst</u> Signature</p> <p><u>Barbara G Ernst</u> Name</p> <p><u>30,377</u> Registration Number</p> | | |

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Our Ref: FP2262/GM

Your Ref: PCT/SG2004/000168

CONFIRMATION

16 June 2005

FAX COPY – CONFIRMATION BY MAIL

No. of Pages 2

Your Fax No. 001 61 2 6285 3929

Our Fax No. (65) 6227 3898

Dear Sirs,

Re: PCT Patent Application No. PCT/SG2004/000168
entitled CHOLESTEROL BIOSYNTHESIS PATHWAY MODULATORS AND USES
THEREOF
in the name National University of Singapore

We refer to the Written Opinion of the International Preliminary Examining Authority of 5 May 2005.

The applicant respectfully disagree with the Examiner's comments. In response to the Examiner's objections in the Written Opinion, the applicant wishes to make the following written submissions.

Inventive Step

The Examiner has opposed to claim 24 and some of its dependent claims with respect to inventive step, citing D1 (Indian Heart Journal, 1986, Vol. 38, No.5, pages 369-372) as prior art. In particular, claim 24 relates to an isolated peptide having the function of HMGCoA reductase inhibitor, phosphomevalonate inhibitor, which reduces the accumulation of cholesterol and/or the level of serum cholesterol and wherein the peptide has a molecular weight of 16803 Da, 16790 Da, 16791 Da or 17211 Da.

D1 describes how the authors had induced acute myocarditis using red scorpion (*Buthus tamulus*) venom in dogs, as a model to study the effects of scorpion stings. The crude venom at 4mg/kg was injected intravenously in dogs to create the acute myocarditis. Blood was collected 40 minutes after the venom administration and was processed for serum total cholesterol, free fatty acids and phospholipids.

Based on the ECG findings, the authors reported an initial phase of hypertension followed by a hypotensive phase and the authors claimed that these effects were due to the release of massive amounts of catecholamines due to the venom administration. They further reported that the catecholamines activate specific lipases in adipose tissue and muscle, which then breaks down triglycerides to free fatty acids and glycerol. The increase in serum level of phospholipids was due to the epinephrine release during the envenomation.

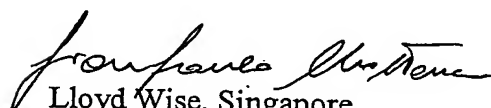
As such, the authors were creating a model to study scorpion envenomation in dog and in the process observed that the release of catecholamines and epinephrines by the venom was responsible for acute myocarditis and the altered serum lipid profiles. However, there was no indication or suggestion of any protein or compound, nor its function or activity, in the venom that could be responsible for the reduction in total cholesterol and related products.

Therefore, a person skilled looking at whole the content of D1 would have not found any indication nor suggestion to look for a particular peptide in scorpion venom, let alone a peptide having a molecular weight of 16803 Da, 16790 Da, 16791 Da or 17211 Da. On the contrary, the skilled person was suggested that catecholamines and epinephrines were responsible of the altered serum lipid profile. Therefore, it would not have been obvious to a person skilled in the art to isolate a peptide having the above-mentioned molecular weights from scorpion venom.

In view of the above, the applicant respectfully requests that the Examiner reconsiders his opinion and finds that claims 24, 26-28, 31-36, 39 and 40 indeed have an inventive step.

We look forward to receiving the International Preliminary Report on Patentability (IPRP) in due course.

Yours faithfully,


Lloyd Wise, Singapore
Gianfranco Matteucci